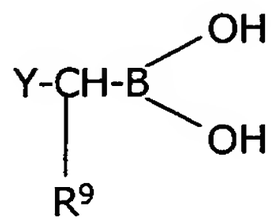
Amendments to the Claims

This listing of claims will replace all prior versions, and listings of claims in the application.

1. (Original) An oral dosage form of a compound selected from boronic acids which have a neutral thrombin P1 domain linked to a hydrophobic moiety capable of binding to the thrombin S2 and S3 subsites, and salts, prodrugs and prodrug salts of such acids, the dosage form comprising a solid phase formulation comprising the compound and being adapted for reconstitution of the formulation to form a liquid preparation.

2. (Currently amended) [[A]] The dosage form of claim 1 wherein the thrombin P1 domain comprises a neutral aminoboronic acid residue.

3. (Currently amended) [[A]] The dosage form of claim 1 wherein the boronic acid is of formula (I):



(I)

wherein

Y comprises a moiety which, together with the fragment $-CH(R^9)-B(OH)_2$, has affinity for the substrate binding site of thrombin; and

R^9 is a straight chain alkyl group interrupted by one or more ether linkages and in which the total number of oxygen and carbon atoms is 3, 4, 5 or 6 or R^9 is $-(CH_2)_m$-W where m is from 2, 3, 4 or 5 and W is –OH or halogen, wherein halogen is F, Cl, Br or I. ~~(F, Cl, Br or I).~~

4. (Currently amended) [[A]] The dosage form of claim 3 wherein R^9 is an alkoxyalkyl group.

5. (Currently amended) [[A]] The dosage form of claim 3 wherein Y comprises

an amino group bonded to structural fragment $-CH(R^9)-B(OH)_2$, and

a hydrophobic moiety which is linked to said amino group and which, together with said structural fragment, has affinity for the substrate binding site of thrombin.

6. (Currently amended) [[A]] The dosage form of claim 5 ~~any of claims 3 to 5~~ wherein Y comprises an amino acid which binds to the S2 subsite of thrombin, the amino acid being N-terminally linked to a moiety which binds the S3 subsite of thrombin.

7. (Currently amended) [[A]] The dosage form of claim 6 wherein Y is an optionally N-terminally protected dipeptide which binds to the S3 and S2 binding sites of thrombin and the peptide linkages in the acid are optionally and independently N-substituted by a C_1-C_{13} hydrocarbyl optionally containing in-chain or in-ring nitrogen,

oxygen or sulfur and optionally substituted by a substituent selected from halo, hydroxy and trifluoromethyl~~, and optionally wherein said dipeptide is N-terminally protected and/or all the peptide linkages in the acid are unsubstituted~~.

8. (Currently amended) [[A]] The dosage form of claim 7 wherein the S3-binding amino acid residue is of (R) configuration, the S2-binding residue is of (S) configuration, and the fragment $-NHCH(R^9)-B(OH)_2$ is of (R) configuration.

9. (Currently amended) [[A]] The dosage form of claim 1 ~~any of claims 1 to 8~~ wherein said compound is a pharmaceutically acceptable base addition salt of a said acid.

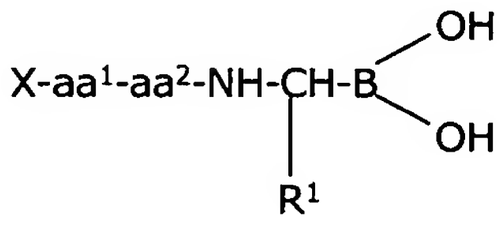
10. (Currently amended) An oral pharmaceutical dosage form adapted to be reconstituted either

prior to administration into a liquid for oral administration, or

in the mouth,

and comprising a compound selected from boronic acids of formula (III) and salts, prodrugs and prodrug salts thereof:

where:



(III)

X is H (to form NH_2) or an amino-protecting group;

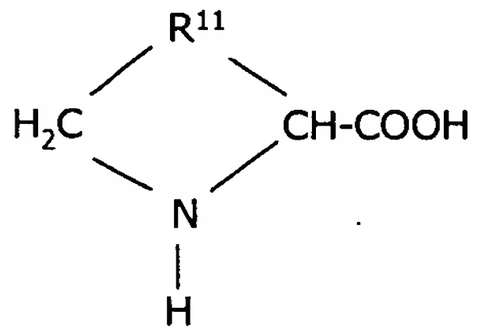
aa^1 is an amino acid having a hydrocarbyl side chain containing no more than 20 carbon atoms and comprising at least one cyclic group having up to 13 carbon atoms;

aa^2 is an imino acid having from 4 to 6 ring members; and

R^1 is a group of the formula $-(CH_2)_s-Z$, where s is 2, 3 or 4 and Z is –OH, –OMe, –OEt or halogen, wherein halogen is F, Cl, Br or I. ~~(F, Cl, Br or I).~~

11. (Currently amended) [[A]] The dosage form of claim 10 wherein aa^1 is selected from Phe, Dpa and wholly or partially hydrogenated analogues thereof~~, and optionally is selected from Dpa, Phe, Dcha and Cha, e.g. is (R) Phe or (R) Dpa~~.

12. (Currently amended) [[A]] The dosage form of claim 10 ~~or claim 11~~ wherein aa^2 is a residue of an imino acid of formula (IV)



(IV)

where R^{11} is $-CH_2-$, $-CH_2-CH_2-$, $-CH_2=CH_2-$, $-S-CH_2-$, $-S-C(CH_3)_2-$ or $-CH_2-CH_2-CH_2-$, which residue ~~group~~, when the ring contained therein is 5- or 6- membered, is optionally substituted at one or more $-CH_2-$ groups by from 1 to 3 C_1-C_3 alkyl groups ~~and optionally aa^2 is an (S) proline residue, e.g. aa^1-aa^2 is (R) Phe (S) Pro~~.

13. (Currently amended) [[A]] The dosage form of claim 10 ~~any of claims 10 to 12~~ wherein aa^1 is of (R)-configuration, ~~and/or~~ aa^2 is of (S)-configuration ~~and/or~~ and the fragment -NH-CH(R^1)-$B(OH)_2$ is of (R)-configuration.

14. (Currently amended) [[A]] The dosage form of claim 10 ~~any of claims 10 to 13~~ wherein R^1 is 2-bromoethyl, 2-chloroethyl, 2-methoxyethyl, 3-bromopropyl, 3-chloropropyl or 3-methoxypropyl~~, e.g. is 3-methoxypropyl~~.

15. (Currently amended) [[A]] The dosage form of claim 10 ~~any of claims 10 to 14~~ where X is R^6-$(CH_2)_p$-C(O)-, R^6-$(CH_2)_p$-$S(O)_2$-, R^6-$(CH_2)_p$-NH-C(O)- or R^6-$(CH_2)_p$-O-C(O)- wherein p is 0, 1, 2, 3, 4, 5 or 6 and R^6 is H or a 5 to 13-membered cyclic group optionally substituted by one or more ~~(e.g. 1, 2, 3, 4 or 5)~~ halogens ~~(e.g. F), for example at least at the 4-position,~~ and/or by 1, 2 or 3 substituents selected from amino, nitro, hydroxy, a C_5-C_6 cyclic group, C_1-C_4 alkyl and C_1-C_4 alkyl containing, and/or linked to the cyclic group through, an in-chain O, the aforesaid alkyl groups optionally being substituted by a substituent selected from halogen, amino, nitro, hydroxy and a C_5-C_6 cyclic group~~, and optionally said 5 to 13-membered cyclic group is aromatic or heteroaromatic, e.g. is phenyl or a 6-membered heteroaromatic group, for example X is benzyloxycarbonyl~~.

16. (Currently amended) [[A]] The dosage form of claim 10 ~~or claim 15~~ wherein the boronic acid is of formula (VIII):

X-(R)-Phe-(S)-Pro-(R)-Mpg-$B(OH)_2$ (VIII).

17. (Currently amended) [[A]] The dosage form of claim 9 ~~any of claims 9 to 16~~ wherein the salt comprises a salt of the boronic acid with a metal.

18. (Currently amended) [[A]] The dosage form of claim 17 wherein the metal comprises an alkali metal ~~salt, e.g. sodium, potassium or lithium~~.

19. (Currently amended) [[A]] The dosage form of claim 1 ~~any of claims 1 to 18~~ which comprises boronate ions derived from the ~~peptide~~ boronic acid and has a stoichiometry consistent with the boronate ions carrying a single negative charge.

20. (Currently amended) [[A]] The dosage form of claim 1 ~~any of claims 1 to 19~~ which comprises:

a pharmaceutical formulation which contains said compound and is in the form of powder or granules; and

a sealed container in which the formulation is contained and from which the formulation is to be dispensed for reconstitution.

21-22. (Canceled)

23. (Currently amended) [[A]] The dosage form of claim 20 ~~any of claims 20 to 22~~ wherein the container is a sachet.

24. (Currently amended) [[A]] The dosage form of claim 1 ~~any of claims 1 to 19~~ wherein the solid phase ~~which comprises a pharmaceutical~~ formulation ~~which~~ is a pharmaceutical formulation in the form of an effervescent tablet which contains ~~said compound and~~ an effervescent system, or is a fast melt pharmaceutical formulation.

25. (Canceled)

26. (Currently amended) [[A]] The dosage form of claim 20 ~~any of claims 20 to 25~~ which comprises from about 0.2 to about 1.5 mol of the compound, calculated on the basis of the boronic acid~~, e.g. about 0.35 to about 1 mol~~.

27. (Canceled)

28. (Currently amended) [[A]] The dosage form of claim 1 ~~any of claims 1 to 23, or claims 26 or 27 when not dependent on claim 26,~~ which is adapted to be reconstituted to form a solution having a volume of from about 50ml to about 150ml.

29. (Original) A pharmaceutical formulation comprising a pharmaceutically acceptable base addition salt of the acid Cbz-(R)-Phe-(S)-Pro-(R)-Mpg-$B(OH)_2$, the formulation being in the form of a powder or granules in a sachet or of an effervescent tablet.

30. (Currently amended) A method of making an oral dosage form for preventing thrombosis, comprising:

reacting a boronic acid which has a neutral thrombin P1 domain linked to a hydrophobic moiety capable of binding to the thrombin S2 and S3 subsites with a base selected from the group consisting of basic metal compounds~~, e.g. a metal hydroxide or carbonate,~~ and organic nitrogen-containing compounds having a pKb of at least 7, to form a reaction product; and

formulating the reaction product into a solid phase formulation which comprises the reaction product and is adapted for reconstitution of the formulation to form a liquid preparation.

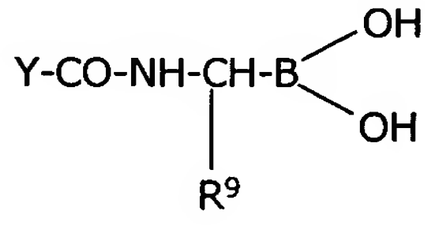
31. (Currently amended) ~~A use of a compound as defined in any of claims 1 to 19~~ A method for the manufacture of a medicament to be reconstituted to form a drinkable preparation, comprising making the medicament with a compound as defined in claim 1 ~~e.g. a drinking solution~~.

32-33. (Canceled)

34. (Currently amended) A method of preparing an anticoagulant preparation, comprising reconstituting, into a liquid preparation for oral administration ~~and preferably a drinkable preparation,~~ a solid phase formulation comprising:

a) a first species selected from the group consisting of a [[(a)]] boronic acid ~~acids~~ of formula (I) below, [[(b)]] said acid when in the form of a boronate anion thereof,

~~and (c) any~~ an equilibrium form of said boronic acid and of said boronate ion ~~of the aforegoing (e.g. an anhydride)~~, and combinations thereof:



(I)

wherein

Y comprises a hydrophobic moiety which, together with the aminoboronic acid residue -$NHCH(R^9)$-$B(OH)_2$, has affinity for the substrate binding site of thrombin; and

R^9 is a straight chain alkyl group interrupted by one or more ether linkages and in which the total number of oxygen and carbon atoms is 3, 4, 5 or 6 or R^9 is $-(CH_2)_m$-W where m is ~~from~~ 2, 3, 4 or 5 and W is –OH or halogen, wherein halogen is F, Cl, Br or I ~~(F, Cl, Br or I)~~; and

(b) a second species selected from the group consisting of pharmaceutically acceptable metal ions~~, said metal ions having a valency of n~~, and strongly basic organic nitrogen-containing compounds.

35. (Currently amended) A method of inhibiting thrombin in the treatment of disease, comprising administering perorally to a subject in need thereof a therapeutically effective amount of a compound as defined in claim 1 ~~any of claims 1 to 19~~, said compound being put into solution or suspension from a solid phase formulation prior to the compound entering the stomach.

36. (Currently amended) The method of claim 35, wherein the compound ~~salt~~ is put into solution or suspension by reconstituting with a liquid prior to administration or in saliva in the mouth.

37. (Currently amended) A method of preventing thrombosis in the haemodialysis circuit of a patient, comprising reconstituting into a drinkable preparation a solid formulation comprising a salt as defined in claim 9 ~~any of claims 9 to 19~~, and orally administering the drinkable preparation.

38-39. (Canceled)

40. (Currently amended) A method of preventing deep vein thrombosis during an airplane flight in a subject ~~at risk of developing such thrombosis~~, comprising administering to the subject a therapeutically effective amount of a compound as defined in claim 1 ~~any of claims 1 to 19~~.

41-42. (Canceled)

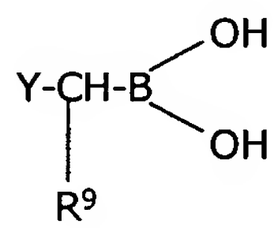
43. (New) A method of preventing thrombosis in intermittent apheresis comprising administering a therapeutically effective amount of a compound as defined in claim 1, wherein said intermittent apheresis is not hemodialysis.

44. (New) The method of claim 43, wherein the intermittent apheresis is extracorporeal liver detoxification.

45. (New) The method of claim 43, wherein the compound is an oral medicament or is a parenteral medicament.

46. (New) A method for the prevention of thrombosis in the haemodialysis circuit of a patient undergoing haemodialysis, comprising administering a therapeutically effective amount of a compound selected from boronic acids which have a neutral thrombin P1 domain linked to a hydrophobic moiety capable of binding to the thrombin S2 and S3 subsites, and salts, prodrugs and prodrug salts of such acids, the compound not being a base addition salt of such a boronic acid.

47. (New) The method of claim 46 wherein the boronic acid is of formula (I):



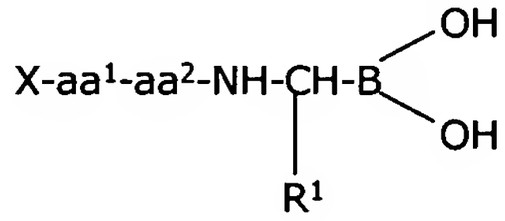
(I)

wherein

Y comprises a moiety which, together with the fragment $-CH(R^9)-B(OH)_2$, has affinity for the substrate binding site of thrombin and R^9 is an alkoxyalkyl group, and wherein Y comprises an amino acid which binds to the S2 subsite of thrombin, the amino acid being N-terminally linked to a moiety which binds the S3 subsite of thrombin, the

S3-binding amino acid residue is of (R) configuration, the S2-binding residue is of (S) configuration, and the fragment $-CH(R^9)-B(OH)_2$ is of (R) configuration.

48. (New) The method of claim 46 wherein the boronic acid is of formula (III):



(III)

where:

X is H (to form NH_2) or an amino-protecting group;

aa^1 is an amino acid having a hydrocarbyl side chain containing no more than 20 carbon atoms and comprising at least one cyclic group having up to 13 carbon atoms;

aa^2 is an imino acid having from 4 to 6 ring members;

R^1 is a group of the formula $-(CH_2)_s-Z$, where s is 2, 3 or 4 and Z is –OH, –OMe, –OEt or halogen, wherein halogen is F, Cl, Br or I.

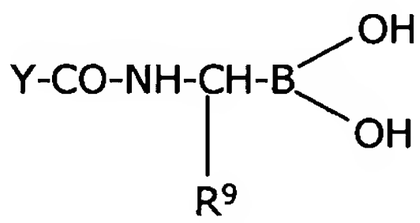
49. (New) The method of claim 46 wherein the boronic acid is a compound designated TRI 50c of the following formula

Cbz-(R)-Phe-(S)-Pro-(R)-Mpg-$B(OH)_2$.

50. (New) The dosage form of claim 10 wherein the prodrugs are boronic acid derivatives capable of hydrolysing to release the free boronic acid.

51. (New) A method for preventing flight deep vein thrombosis [[DVT]] or thrombosis in intermittent apheresis, wherein said intermittent apheresis is not hemodialysis, comprising administering a therapeutically effective amount of a composition of matter comprising

a) a first species selected from the group consisting of a boronic acid of formula (I) below, said acid when in the form of a boronate anion thereof, an equilibrium form of said boronic acid and of said boronate ion, and combinations thereof:



(I)

wherein

Y comprises a hydrophobic moiety which, together with the aminoboronic acid residue $-NHCH(R^9)-B(OH)_2$, has affinity for the substrate binding site of thrombin; and

R^9 is a straight chain alkyl group interrupted by one or more ether linkages and in which the total number of oxygen and carbon atoms is 3, 4, 5 or 6 or R^9 is $-(CH_2)_m-W$ where m is 2, 3, 4 or 5 and W is –OH or halogen, wherein halogen is F, Cl, Br or I; and

(b) a second species selected from the group consisting of pharmaceutically acceptable metal ions and strongly basic organic nitrogen-containing compounds.

52. (New) An aqueous solution comprising a pharmaceutically acceptable base addition salt of a boronic acid which has a neutral thrombin P1 domain linked to a hydrophobic moiety capable of binding to the thrombin S2 and S3 subsites, the solution having a pH of about 9 or more.

53. (New) The solution of claim 52 wherein the pH is about 9 to about 9.5.

54. (New) An aqueous solution comprising a pharmaceutically acceptable base addition salt of a boronic acid which has a neutral thrombin P1 domain linked to a hydrophobic moiety capable of binding to the thrombin S2 and S3 subsites and a pharmaceutically acceptable organic acid, the solution having a pH of from about 4 to about 8.